REMARKS

I. The Subject Matter of the Claims

In general, the subject matter of the claims relates to methods for detecting ICAM-4 in a sample and to monoclonal antibodies specific for human ICAM-4 protein.

II. Patentability Arguments

A. The Rejections of Claim 27 Under 35 U.S.C. §112, First Paragraph, May Properly Be Withdrawn

The Examiner maintains the rejection of claim 27 under 35 U.S.C. §112, first paragraph, as assertedly lacking written description, objecting to the phrase "specifically immunoreactive." The Examiner asserts that the Applicants have defined the term "specifically immunoreactive" as conferring exclusive binding of the monoclonal antibody to only a particular antigen, and that this is inconsistent with the art-recognized teaching of antibody binding. The Examiner contends that because Applicants have not tested the monoclonal antibody against every epitope in nature, it cannot be deemed specific for only ICAM-4.

Applicants respectfully disagree. Applicants previously referred to an art-accepted manual for producing monoclonal antibodies, Harlow *et al*, "Antibodies: A Laboratory Guide," (1988) to obtain the accepted definition of "specific binding." Applicants stated previously that the "Harlow *et al.*" book sets out that a specifically binding antibody is one that only recognizes the appropriate antigen (Harlow *et al.*, Ch. 5) and has a defined, unique specificity (Harlow *et al.*, Ch. 6, "Monoclonal Antibodies"), which does not imply exclusive binding as suggested by the Examiner.

Applicants appreciate and recognize that antibodies bind specific epitopes within a protein, and that an antibody may cross-react if similar epitopes are found in other proteins. However, page 8, lines 2-5, of the specification clearly sets out what Applicants mean by specific ICAM-4 binding by an antibody, "i.e. non-reactive with the ICAM-1, ICAM-2, and ICAM-R intracellular adhesion molecules to which ICAM-4 is structurally related." Applicants recognize that these proteins share varied degrees of structural homology (see specification page 37, line 23 to page 38, line 3), and define an ICAM-4 specific binding protein (page 8, lines 2-5) as one that

does not interact with these structurally similar proteins. The claim further recites that the antibody reacts with a human ICAM-4. Thus, an antibody that cross-reacts with another molecule, specifically a structurally related ICAM molecule as stated above, or a non-human ICAM-4, lies outside the scope of the claim. An example of such an immunospecific monoclonal antibody is found for example, in Oka *et al.* (*Neuroscience* 35:93-103, 1990), which discloses a monoclonal antibody to rabbit telencephalin that did not cross-react with the protein in other species (see Oka page 94, column 1). Oka further defines that the monoclonal antibody is immunochemically specific for the telencephalin protein (Oka, page 96, column 1), which is consistent with the definition put forth herein.

The Examiner raises new objections to claim 27 under 35 U.S.C. §112, first paragraph, based on Applicants' amendment, for assertedly lacking written description of a monoclonal antibody that binds to a fragment of ICAM-4 and variants of human ICAM-4 encoded by polynucleotides which hybridize to the polynucleotide of SEQ ID NO: 27.

Claimed monoclonal antibodies 179H and 179I were generated against domains 1-3 of the full-length ICAM-4 protein, and specifically bind this fragment of the ICAM-4 protein, thereby providing support for a monoclonal antibody that binds a fragment of ICAM-4. Further, at page 7, lines 16-28, the specification describes variants and analogs contemplated by the invention and the specification expressly discloses that monoclonal antibodies which specifically bind these variants are contemplated by the invention [see page 7, line 29 to page 8, line 5].

Additionally, the specification provides support for monoclonal antibodies that bind natural variants of the human ICAM-4 protein. Examples 16 and 18 demonstrate that the ICAM-4 monoclonal antibody of the invention binds ICAM-4 in patients recently suffering from stroke, those with neurological disorders such as epilepsy, AIDS patients, or healthy volunteers, suggesting that anti-ICAM-4 monoclonal antibody can detect the natural variations of the protein in the human population and in different disease states.

Applicants have provided specific examples of ICAM-4 variants and fragments bound by the ICAM-4 monoclonal antibodies, and demonstrated that a

monoclonal antibody binds to ICAM-4 isolated from numerous individuals all expressing at least one form of ICAM-4 hybridizing fragment or variant.

The Examiner contends that Applicants have not supported the genus of anti-ICAM-4 antibodies, and cites an example wherein a bovine sequence was insufficient support for the entire genus of mammalian FGF genes (Fiddes v Baird, 30 USPQ2d 1481). However, Fiddes addresses insufficiency of disclosure of polynucleotide sequences, not antibodies, which are at issue at present. Recent court decisions indicate that "the PTO would find compliance with § 112, P 1, for a claim to an 'isolated antibody capable of binding to antigen X,' notwithstanding the functional definition of the antibody, in light of 'the well defined structural characteristics for the five classes of antibody, the functional characteristics of antibody binding, and the fact that the antibody technology is well developed and mature.'" Enzo Biochem v. Gen-Probe, Inc., 323 F.3d 956, 964 (Fed. Cir. 2002).

Additionally, the court adopted the USPTO Guidelines "as persuasive authority for the proposition that a claim directed to 'any antibody which is capable of binding to antigen X' would have sufficient support in a written description that disclosed 'fully characterized antigens.' Synopsis of Application of Written Description Guidelines, at 60, available at http://www.uspto.gov/web/menu/written.pdf (last visited Jan. 16, 2003). Therefore, based on our past precedent, as long as an applicant has disclosed a 'fully characterized antigen,' either by its structure, formula, chemical name, or physical properties, or by depositing the protein in a public depository, the applicant can then claim an antibody by its binding affinity to that described antigen." Noelle v. Lederman, 355 F.3d 1343 at 1349 (Fed. Cir. 2004).

Applicants have provided a "fully characterized" ICAM-4 antigen, with full chemical structure, as well as fragments and variants thereof. Thus, Applicants have fulfilled the written description requirement for antibodies that bind these fully characterized antigens. As such, Applicants submit that the rejection of claim 27 under 35 U.S.C. § 112 may properly be withdrawn.

B. The Rejection of Claim 27 Under 35 U.S.C. §103(a), May Properly Be Withdrawn

The Examiner contends that claim 27 is assertedly unpatentable under 35 USC § 102(b) in light of the disclosure of Oka, in view of Yoshihara, and further in view of Goding. Applicants submit that this should be a rejection under 35 USC § 103(a) as set forth in the previous Office Action of November 18, 2003.

The Examiner asserts that based on Oka, a worker of skill would have reason to expect that a human ICAM-4 exists and could easily isolate a human ICAM-4 using the polyclonal antibody of Oka. The Examiner also contends that it is not persuasive that the claim is directed to SEQ ID NO: 27 or 28 or fragments thereof because it encompasses fragments as small as 6 amino acids.

Applicants respectfully disagree. The present application is the first disclosure of a human ICAM-4, which is defined by the polynucleotide sequence set out in SEQ ID NO: 27 and amino acid sequence of SEQ ID NO: 28. To the extent that the worker of ordinary skill could have speculated that a human ortholog might exist, this same worker certainly would not have speculated that such human protein would have the amino acid sequence set out in SEQ ID NO: 28.

Additionally, the claims are directed to a monoclonal antibody that binds the human ICAM-4 protein disclosed herein, or fragment or variant thereof. The Examiner implies that a monoclonal antibody that binds the presently disclosed ICAM-4 and fragments thereof is obvious because a worker of skill would use the polyclonal antibody of Oka to isolate an human ICAM-4 protein that would necessarily have all the fragments of the presently identified ICAM-4, and further implies that this protein would necessarily produce monoclonal antibodies with the same properties and specificity as the claimed monoclonal antibodies. Applicants submit that the Examiner provides no experimental evidence to support this assertion.

The Examiner argues that because Oka discloses a polyclonal antibody that binds to a protein in several mammalian species, it would naturally lead a worker of skill in the art to the exact sequence of ICAM-4 disclosed in the present application, or at least a sequence close enough to the presently disclosed sequence, and monoclonal antibodies specific for said sequence.

Oka provides no definitive evidence that the protein bound by the polyclonal rabbit sera in the telencephalon of other mammalian species is indeed an ortholog to rabbit telencephalin. None of the reactive proteins were sequenced by Oka to confirm their identity as telencephalin, and not all of the species tested by Oka have a known sequence of the telencephalin protein. The Examiner is assuming that there is a single ICAM in the telencephalon reactive with the polyclonal sera, and that multiple proteins with a common epitope are not cross-reacting with the sera. The possibility exists, however, that multiple proteins are expressed in the telencephalon of the tested mammals that include an epitope bound by the polyclonal antisera.

Evidence of polyclonal antibodies binding multiple proteins is common in the art. For example, Tuslisani et al (*J. Biol. Che*m. 263:5408-17, 1988, enclosed herewith) indicate that a polyclonal antibody to mannosidase IA immunoprecipitates both mannosidase IA and IB isoforms (Tusliani, page 5414). Additionally, Arlotto et al (*Arch. Biochem. Biophys.* 270:441-57, 1989, abstract enclosed) demonstrate that a polyclonal antibody against liver cytochrome p450a of immature rats, preabsorbed against cross-reactive species, identified three additional proteins in mature rat liver extract. Further, Rogel et al. (*J Biol Chem* 263:13310-6. 1988, disclose polyclonal antibodies to *B. pertussis* adenylate cyclase which bind enzymes of 200 and 47 kD), and Maenpaa et al. (*Biochem. Pharmacol.* 45:899-907, 1993, discloses polyclonal antibodies against mouse liver cytochrome P450 isoforms which bind to 2-3 different human proteins) (abstracts enclosed), also demonstrate that polyclonal antibodies to one protein identify multiple isoforms of a related protein. These observations illustrate that a worker of ordinary skill in the art using the antibody of Oka could have isolated several related proteins that bind to the non-exclusive, anti-rabbit telencephalin polyclonal antibody, and it is possible that none would be the human ICAM-4 disclosed herein.

Applicants submit that the Examiner's rejection of claim 27 under 35 U.S.C. §103 (a) as obvious in view of Oka, in light of Yoshihara and Goding, may properly be withdrawn.

VI. Conclusion

In view of the amendments and remarks made herein, Applicants submit that claim 27 is in condition for allowance and respectfully request expedited notification of the same.

Respectfully submitted,

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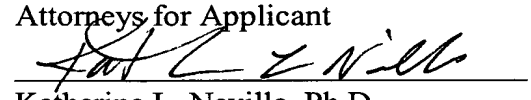
December 2, 2004 By 

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